Department: **UAMS Institutional Review Board**
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Section: **Consent**
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Subject: Informed Consent

Informed consent is one of the primary ethical requirements underpinning research with human subjects; it reflects the basic principle of respect for persons. It is too often forgotten that informed consent is an ongoing process, not a piece of paper or a discrete moment in time. Informed consent assures that prospective human subjects will understand the nature of the research and can knowledgeably and voluntarily decide whether or not to participate. This assurance protects all parties -- both the subject, whose autonomy is respected, and the investigator, who otherwise faces legal hazards. The "proxy consent" of someone other than the subject is not the same as the subject's own consent, although it may be an acceptable substitute when a subject is unable to give informed consent. Federal Policy consent requirements are provided in 45CFR46.116 and 45 CFR46.117; FDA consent requirements are provided in 21CFR50.20-27 and 21CFR56.109.

OVERVIEW

The **Nuremberg Code**, developed by the International Military Tribunal that tried Nazi physicians for the "experiments" they performed on unconsenting inmates of concentration camps, was the first widely recognized document to deal explicitly with the issue of informed consent and experimentation on human subjects. The first principle of the code states:

The voluntary consent of the human subject is absolutely essential. This means that the person involved should have legal capacity to give consent; should be so situated as to be able to exercise free power of choice without the intervention of any element of force, fraud, deceit, duress, over-reaching, or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him to make an understanding and enlightened decision. This latter element requires that before the acceptance of an affirmative decision by the experimental subject there should be made known to him the nature, duration and purpose of the experiment; the method and means by which it is to be conducted; all inconveniences and hazards reasonably to be expected; and the effects upon his health or person which may possibly come from his participation in the experiment.

Although the elements of informed consent (*i.e.*, full disclosure, adequate comprehension, voluntary choice) are easy to enumerate, recent empirical studies suggest they are not so easy to achieve. Even the best intentions do not ensure against failures of communication --information may be poorly conveyed or subjects may forget (if indeed they ever understood) that they are involved in a research project. Enhancing the likelihood that informed consent will take place is a challenge to which IRBs should respond with imagination and good judgment. When the proposed research will involve vulnerable subjects or the research design involves incomplete disclosure or deception, the challenges to the IRB are even greater. Certain populations (*e.g.*, children or

mentally retarded individuals) may not be able to understand the required information, whereas other populations (*e.g.*, prisoners or institutionalized individuals) are so situated that the voluntariness of their consent may be in doubt. Hospitalized patients, particularly those who are seriously ill or undergoing emergency treatment, may also need special protection. Problems raised by the involvement of some vulnerable populations are discussed in the “Special Populations” section of this guidebook.

IRB CONSIDERATIONS

The issues discussed in this section are general IRB considerations regarding informed consent, and they apply generally to the review of research that involves human subjects. Problems surrounding the use of deception or incomplete disclosure are discussed near the end of this section under the headings "Exceptions," "Deception and Incomplete Disclosure," and "Placebos, Randomization, and Double-Masked Clinical Trials."

The Regulations. The federal regulations require that certain information must be provided to each subject [45 CFR 46.116; 21 CFR 50.20-23; 38 CFR16.116]:

1. A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental.
2. A description of any reasonably foreseeable risks or discomforts to the subject.
3. A description of any benefits to the subject or to others which may reasonably be expected from the research.
4. A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject.
5. A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained.
6. For research involving **more than minimal risk**, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained. *Note: This may be left out of studies that do not involve treatments, which are only minimal risk.*
7. An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject and
8. A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

The regulations further provide that the following additional information be provided to subjects, **where appropriate**] Note: The IRB may waive these requirements where **not** appropriate or applicable. See the sections below:

1. A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable.

2. Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent.

3. Any additional costs to the subject that may result from participation in the research (see Section 14, Recruitment Practices).

4. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.

5. A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject (see Section 14, Recruitment Practices).

6. The approximate number of subjects involved in the study.

Further institutionally required elements in the Informed Consent and sample informed consent documents can be found in the Investigator's Checklist for Informed Consent.

An IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent set forth above, or waive the requirement to obtain informed consent provided the IRB finds and documents that

1. The research or demonstration project is to be conducted by or subject to the approval of state or local government officials and is designed to study, evaluate, or otherwise examine: (i) public benefit or service programs; (ii) procedures for obtaining benefits or services under those programs; (iii) possible changes in or alternatives to those programs or procedures; or (iv) possible changes in methods or levels of payment for benefits or services under those programs and

2. The research could not practicably be carried out without the waiver or alteration.

An IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent set forth in this section, or waive the requirements to obtain informed consent provided the IRB finds and documents that:

1. The research involves no more than minimal risk to the subjects.

2. The waiver or alteration will not adversely affect the rights and welfare of the subjects.

3. The research could not practicably be carried out without the waiver or alteration and

4. Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

The informed consent requirements in this policy are not intended to preempt any applicable Federal, State, or local laws which require additional information to be disclosed in order for informed consent to be legally effective.

Nothing in this policy is intended to limit the authority of a physician to provide emergency medical care, to the extent the physician is permitted to do so under applicable Federal, State, or local law.

Adequacy of the Content. One of the IRB's most important activities is evaluating the information to be provided to potential subjects in light of the risks and benefits of the proposed research procedures. Each IRB member brings a different perspective to this review. Certain expert members may be able to correct the technical information or identify omissions in the consent documents provided by the investigators. Other members may add their reactions to the way information is provided or question the adequacy of the information. Whether or not the information is deemed "adequate" depends partly on the impression being conveyed (*e.g.*, whether it is clear that a procedure is to be done for research purposes).

In making a judgment concerning what information should be disclosed in the informed consent process, the IRB should attempt to view the matter from the subject's perspective by asking what facts the subjects might want to know before deciding whether or not to participate in the research. Information could be deemed "material" if it might influence the decision of any reasonable person. For example, the risk of death from cardiac catheterization might be statistically small, and, therefore, seem unimportant to an investigator, but the risk may loom large for people invited to undergo the procedure for the benefit of others. Research in sensitive areas such as child abuse, illegal activities such as drug or alcohol abuse, or reportable communicable diseases such as HIV, also may pose risks to subjects about which they should be informed. Where the potential for the need to report such information to authorities exists, subjects should be so informed before agreeing to participate in the study. Depending on the circumstances, potential subjects may also feel it is "material" to be informed about additional costs that might arise during the course of the research, the identity of the research sponsor, any circumstances that would make it difficult or dangerous to withdraw from the research, or the amount or kind of inconvenience involved.

Expression. IRBs must ensure that information will be presented to prospective subjects in language they can understand. How well subjects understand that information will vary according to the population from which subjects will be drawn. The medical terms and complex sentences in oral presentations and consent forms often need to be presented in simpler terms -- even for the educated layperson. If the prospective subjects include children, persons whose primary language is not English, or populations with the average of a eighth grade education, the IRB should take special care to ensure that both oral presentations and consent forms are comprehensible to all subjects. In these cases, ordinary language should replace technical terms (*e.g.*, upper extremities are better referred to as arms, hematoma as a bruise, venipuncture as taking blood from your arm with a needle, and so forth).

In addition, **the informed consent may not contain any exculpatory language**: Subjects may not be asked to waive (or appear to waive) any of their legal rights, nor may they be asked to release the investigator, sponsor, or institution (or its agents) from liability for negligence.

Process. It is essential that IRB members think of informed consent not as a form that must be signed, but as an educational process that takes place between the investigator and the prospective subject. No one can guarantee that another person has understood the information presented; one can only inform prospective subjects as clearly as possible. No one can guarantee that another's choice is voluntary; one can only attempt to remove obvious impediments to free choice by being alert to coercive aspects of the consent procedure. In cases where there is reason for special concern about pressure (*e.g.*, when patients are invited to participate in research conducted by their physician, or when students, military personnel, employees, etc., are asked to participate in research conducted by their supervisors), the IRB may require some form of monitoring (such as the presence of an impartial observer). If the research presents significant risk, or if subjects are likely to have difficulty understanding the information to be provided, the IRB may suggest that investigators employ devices such as audiovisual aids, tests of the information presented, or consent advisors.

Documentation. In most cases the federal regulations require that informed consent be documented (45 CFR46.117; 21 CFR50.27; and 38 CFR16.117), but they also provide for some important exceptions. Documentation usually involves the use of a written consent form containing all the information to be disclosed and signed by the subject or the subject's legal representative. It should be reiterated, however, that these documents are not substitutes for discussion. The person who signed the consent form must be given a copy as a reference and reminder of the information conveyed.

A "short form" may sometimes be used [38 CFR16.117(b)(2); 21 CFR50.27(b)(2); 45 CFR]. The use of a short form means that the information is presented without benefit of a written version of the consent document. Before a short form can be used, the IRB must first review and approve a written summary of what will be presented. Each oral presentation must be witnessed by a third person, who must sign both the consent form and a copy of the written summary of the presentation. A copy of the summary must be provided to those who sign the consent form so that they have the information available for future reference [38CFR16117(b)(2)].

Informed Consent And Assent Documents

The informed consent form for an adult must provide signature lines along with dates and time for subject, Principal Investigator (PI), person obtaining consent, and witness. However, the person obtaining consent cannot serve as the witness, although a study team member may serve as the witness. The person serving as the witness is not required to be present during the explanation of the study, but must be present for the signing of the consent document by the subject. The IRB requires the PI’s signature on all subject informed consent documents. The PI may designate someone to explain the consent and does not have to be present when the subject signs the consent but must subsequently sign this document signifying acceptance of the responsibility for all aspects of the study with regards to the enrolled subject.

If children from 7-17 years of age are subjects, signature lines with date and time should also be provided for the child's assent and for the parent(s) consent. If the IRB deems the risk of the study in children to be Pediatric Category 3 or 4, space for both parents' signature must be available

The PI must retain the original signed consent form document in the study file and provide a copy to the subject. The PI must retain copies of the completed consent forms for a period of at least three years following termination of the protocol. The IRB may request the PI to maintain a longer storage period for the executed consent form.

Each subject must be given a copy of the signed informed consent document. A copy of the subject's informed consent must be placed in the medical records. Pharmacies at each institution may also require a copy of the signed informed consent and protocol before dispensing study drugs.

Additionally, the process of informed consent must be documented by an entry in the subject's permanent or medical records. A progress note should be made that includes:

- The date the subject was entered into the study
- The title of the study
- The name of the principal investigator
- The name of the person obtaining the informed consent
- The subject had an opportunity to ask questions about the research and have those questions answered

Deception and Incomplete Disclosure. Sometimes, particularly in behavioral research, investigators plan to withhold information about the real purpose of the research or even to give subjects false information about some aspect of the research. This means that the subject's consent may not be fully informed.

IRBs reviewing research involving incomplete disclosure or outright deception must apply common sense and sensitivity to the problem. They must first decide whether the information to be withheld would influence the decision of prospective subjects about participating in the research. According to the regulations, research should not be permitted at all if the risk to subjects is more than minimal and the subjects are not being informed of things they would consider material to a decision to participate.

A final condition for waiving some or all of the elements of informed consent is that, whenever appropriate, subjects will be given additional pertinent information after they have participated in such a study. The IRB must decide if subjects should be debriefed either after participating in research unwittingly or after knowingly participating in research that involved some form of deception. It is clear that debriefing is appropriate when it contributes to the subject's welfare (*i.e.*, when it corrects painful or stressful misperceptions, or when it reduces pain, stress, or anxiety concerning the subject's performance). There is greater uncertainty over whether it is appropriate to debrief subjects when such a debriefing could itself produce pain, stress, or anxiety (*i.e.*, IRBs must be concerned with cases where debriefing subjects might harm them but failure to debrief subjects would wrong them).

Placebos, Randomization, and Double-Masked Clinical Trials. When the particular therapy a subject receives will be assigned on a scientifically random basis, this selection process must be explained to prospective subjects in language they can understand. Merely telling them that the assignment to treatment will be done randomly, mathematically, or by lottery may not be sufficient. Instead, more of an explanation should be given. In addition, subjects should be told the chances of receiving the various possible treatments, including the chance of receiving a placebo.

It is important that prospective subjects understand that a double-masked design means that neither they, their physicians, nor the investigators treating and evaluating them will know which treatment they have received. If it is important to the research design that neither the investigators nor the subjects know about developing trends in the data, the fact that such developments will not affect their assignment during the course of the study should be communicated to prospective subjects prior to enrollment. Subjects should understand that although they may withdraw from the study at any time, they will not be given any information about which treatment(s) seem to be better or worse until the study is completed.

In double-masked clinical trials, there should be a mechanism for someone other than the investigator to break the code to discover which treatment a particular subject has been given in case the subject experiences a worsening of his or her condition or an adverse effect that requires medical intervention. This procedural safeguard should also be explained to prospective subjects.

Applications and proposals lacking definite plans for involvement of human subjects. Certain types of applications for grants, cooperative agreements, or contracts are submitted to departments or agencies with the knowledge that subjects may be involved within the period of support, but definite plans would not normally be set forth in the application or proposal. These include activities such as institutional type grants when selection of specific projects is the institution's responsibility; research training grants in which the activities involving subjects remain to be selected; and projects in which human subjects' involvement will depend upon completion of instruments, prior animal studies, or purification of compounds. These applications need not be reviewed by an IRB before an award may be made. However, no human subjects may be involved in any project supported by these awards until the project has been reviewed and approved by the IRB.

Research undertaken without the intention of involving human subjects. In the event research is undertaken without the intention of involving human subjects, but it is later proposed to involve human subjects in the research, the research shall first be reviewed and approved by an IRB, as provided in this policy, a certification submitted, by the institution, to the Department or Agency, and final approval given to the proposed change by the Department or Agency (45 CFR46.119).

Consent as a Continuing Process. Consent is not a single event; rather, it is a process. Since subjects always retain the right to withdraw from a research project, their continuing consent is important. IRBs should be aware that subjects often seem to forget they are involved in research or have difficulty distinguishing research interventions from diagnostic and therapeutic interventions. When a research proposal is first approved, the IRB should determine whether consent should be renegotiated as a formal matter during

the course of the research. If renegotiation is required, the frequency and/or events that will trigger this process should be decided upon and made clear to the investigators.

Federal policy also requires that investigators inform subjects of any important new information that might affect their willingness to continue participating in the research (45 CFR46.116). The IRB should also receive copies of any such information conveyed to the subjects. The IRB may require subjects to be reconsented depending upon the nature of the new information presented.

When the proposed subjects are seriously ill, or, for some other reason, might not be able to make decisions about continuing in the research (*e.g.*, children or cognitively impaired individuals), the IRB may suggest that family members be closely involved with the research to evaluate its impact on the subject and to request that the subject be withdrawn from the study if conditions warrant.